DOX and induced cardiotoxicity

Eurasian Clinical and Analytical Medicine Review

DOX's damage

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Abstract

Cancer, one of the most important and deadly diseases of our age, is very difficult to treat. The toxic effects of the drugs used affect the antineoplastic treatment. Anthracyclines are substances that have been proven to be beneficial in cancer chemotherapy in research on microbial products. Doxorubicin is one of the chemotherapeutic agents used in cancer treatment. A broad-spectrum anthracycline is known to have beneficial effects such as antibiotics, as well as adverse effects such as cardiac damage. Doxorubicin causes reactive oxygen radicals in the cell. Today, new natural antioxidant sources are of great importance because of the importance of using antioxidant molecules in the treatment of diseases caused by free radicals. Therefore, it has been shown that the use of antioxidants may be protective against oxidative stress caused by doxorubicin and other cytotoxic drugs. Due to the antioxidant properties of Pistacia vera L. (P. v. L.), which has a high phenolic content, it has been shown in various studies that it is beneficial in anti-inflammatory activity, glycemic control and protection of endothelial function and prevents low oxidation.

Keywords

Cancer, DOX, Cardiotoxicity, Oxidative Stress, Antioxidant

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Introduction

Doxorubicin (DOX) is the hydroxy derivative of an antibiotic of the anthracycline group, derived from the bacterium 'streptomyces pneucetus', a kind of soil fungi. DOX is an effective broad-spectrum antibiotic [1].

Pharmacokinetics of DOX

Conventional DOX is more distributed in plasma and tissues. Absorption takes place within the cell and binds to cellular components that bind more to nucleic acid in cellular Deoxyribonucleic Acid (DNA). Since it cannot cross the blood-brain barrier, it cannot reach the drug concentration in the cerebrospinal fluid, and its absorption in the brain is slower [2]. DOX is administered intravenously because it is not well absorbed in the gastrointestinal tract [1]. Approximately 4-5 days after DOX administration, the drug and its metabolite are excreted in the urine unchanged due to bile [3].

After DOX administration, it is converted to its active metabolite doxorubicinol using a NADPH-dependent aldoreductase enzyme. Doxorubicinol is the active ingredient that provides antineoplastic activity. These reductases are found in erythrocytes, kidney and liver cells [4].

Mechanism of Action of DOX

After Dox is applied, it begins to act on the cell in 4 ways [5]:

- Binding to DNA by forming a complex structure: The DOX trajectory includes a tendency to undergo DNA base pair coupling, breakage of DNA strands, as well as inhibition of RNA synthesis. DOX inhibits the topoisomerase II enzyme, causing DNA expression and apoptosis. When combined with iron, DOX also causes free radical-mediated oxidative action in DNA, further limiting DNA synthesis. Iron chelators such as dexrazoxane can inhibit liberation by inhibiting DOX by inhibiting it with iron [6].
- Inhibition of DNA and RNA polymerases: It impairs DNA replication and RNA transcription by inhibiting the functions of DNA and RNA polymerases.
- Effects on the cell membrane: By binding to the cell membrane, it disrupts the membrane function [7].
- Free radical generation: It reacts with the cytochrome P450 reductase enzyme in the microsomes and forms free oxygen radicals (SOR) [8].

Cardiotoxicity

"Cardiotoxicity", generally defined as "toxicity affecting the heart" [9], is the most common contraindication of cancer chemotherapy [10]. Advances in treatments in the field of cancer led to the opening of the cardio-oncology chapter [11]. Although it is known to have cardiotoxic potential, many chemotherapeutic drugs are still used in cancer treatment. Since these drugs have positive effects such as completely curing patients or prolonging their survival, they continue to be used despite all these complications [12]. Various mechanisms have been proposed for Dox-induced cardiotoxicity or heart failure. The cardiac complication of DOX is directly related to increased oxidative stress in heart tissue. Increased oxidative stress causes the formation of reactive oxygen species that damage the heart muscle and occur due to the reduction of antioxidants and sulfur hydryl groups. In addition, Dox-induced cardiotoxicity includes altered Ca2+ ion levels that cause apoptosis. Apoptosis occurs with the activation of caspases in cardiomyocytes and endothelial cells. [13].

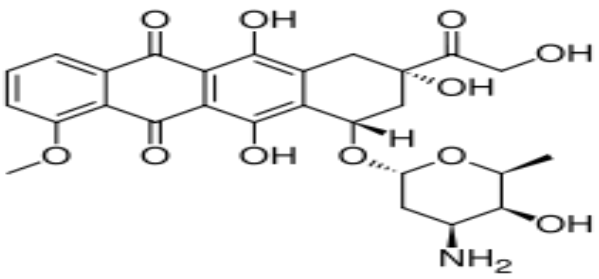

Figure 1. Chemical structure of DOX [1]

DOX and Cardiotoxicity

One of the most important side effects of the drug is cardiac toxicity. Although the mechanism of cardiotoxicity caused by DOX is still not clearly understood, some studies prove that oxidative stress plays a vital role in the mechanism of cardiotoxicity. Decreased antioxidant system and increased oxidative stress play an important role in DOX-induced cardiotoxicity. Co-administered drugs may reduce DOX accumulation in the heart [14].

The most important side effect of production of free radicals after DOX administration is cardiac muscle cell damage [15]. DOX-induced cardiotoxicity is manifested through increased production of SOR and lipid peroxidation in cardiac tissues. Iron complexes of aglycones and anthracyclines promote SOR production [16].

Dox metabolite doxorubicinol removes iron from the catalytic Fe-S cluster of cytoplasmic aconitase (also known as iron-regulating protein-1) and converts this enzyme to a nonfunctional protein [17]. A defect in the iron regulatory gene HFE (Human homeostatic iron regulatory protein) leads to increased iron accumulation in the myocardium and causes cardiotoxicity [18]. The HFE gene plays an important role in the regulation of circulating iron intake [19]. In normal body physiology, cardiomyopathy does not occur because levels of free iron content are not sufficient to bind DOX [20].

In addition, DOX reduces long-chain fatty acid oxidation in the mitochondria of the heart and increases glucose metabolism by showing anaerobic metabolism apart from aerobic metabolism. This shift in metabolism can lead to heart failure or abnormal contraction and relaxation; this shift of metabolism occurs solely due to oxidative stress [21].

Clinical Types of Cardiotoxicity

DOX cardiotoxicity can develop in four different clinical types:

- Acute Cardiotoxicity: Acute anthracycline cardiotoxicity develops during or within hours of administration of the drug. It presents with electrocardiographic abnormalities, arrhythmias, left ventricular dysfunction, heart failure, and, rarely, myocarditis-pericarditis syndrome, which can be fatal [22].
- Subacute Cardiotoxicity: It can occur a few days to a few weeks after administration, and can be seen as acute left heart failure, myocarditis and pericarditis [23].
- Chronic Cardiotoxicity: Late-term toxicity is more common than acute cardiotoxicity in patients receiving anthracycline therapy in the childhood age group and constitutes important health problems. It may develop one to twenty years after completion of treatment. While it may develop in patients who develop and recover from cardiac dysfunction in the subacute period, late-term cardiotoxicity may develop in the long-term follow-up of patients without cardiac involvement in the early period [24].
- Late Cardiotoxicity: Occurs years after chemotherapy is completed. This particular aspect of anthracycline-induced cardiotoxicity is particularly important for adult survivors of pediatric malignancies [25]. It progresses with late-onset ventricular dysfunction and arrhythmias, and it may rarely result in sudden death. In some patients, the first signs of cardiotoxicity may appear too late [26].

Discussion

With the increasing incidence of cancer in recent years, increased doses of antineoplastic drugs and more diverse combinations have been used to provide better toxicity control in these patients [27]. DOX is a chemotherapeutic agent of the anthracycline group used for the destruction of tumors. DOX has the ability to inhibit DNA biosynthesis by DNA intercalation. This drug has high affinity for sites containing Guanine-Cytosine (GC) base pairs and forming hydrogen bonds between DOX and guanine, causing the formation of triple DOX-DNA-topoisomerase II complexes that activate DNA damage responses and eventually cause cell death [28]. Demir et al. evaluated the antioxidant system and lipid peroxidation after the last DOX injection in cardiotoxicity studies induced by DOX, and showed that DOX reduces heart tissue GSH-Px and increases lipid peroxidation products in the chronic process[29]. In recent years, biological markers have been used together with ECHO to detect cardiotoxicity due to anthracyclines. Pro-BNP and troponin I are two of these markers [30]. Troponin (Troponin-I, Troponin-C), CK-MB and brain natriuretic peptide (BNP) markers are the most important markers used to define cardiac damage and to describe the failure that occurs after this damage. DOX has long been thought to act as a pro-oxidative agent, but a large number of studies, demonstrated that this anticancer drug can induce significant oxidative stress within cells [31]. Free radicals, which are the products of oxidation reactions, cause damage to cells and tissues; Eventually, it causes many chronic diseases such as cardiovascular and cancer [32]. Oxidative damage to membrane lipids and other cellular components is thought to be the major factor in the toxicity of DOX and other anthracyclic antibiotics. For this reason, it has been proven in most studies that the use of natural and artificial antioxidants protects against oxidative stress caused by DOX and other drugs in this derivative [33]. While the use of antioxidants has been shown to play a positive role in the treatment of the most common diseases such as CVD and cancer, studies among healthy people and people with heart disease have shown that antioxidants reduce free radicals and protect LDL against oxidation [34].

Dong et al. [35] reported that quercetin, a powerful antioxidant, suppressed DOX-induced cardiotoxicity. Carino-Cortes et al. [36] reported that naringin, with Daunorubicin, an anticancer agent, prevents DNA damage that starts as a result of oxidative stress in hepatocytes and cardiocytes.

In recent years, P.v.L., rich in phenolic compounds, which is a very powerful antioxidant, has been shown to have protective effects against diseases associated with increased oxidative stress as a result of excessive production of free radicals such as cardiovascular diseases (CVD) and cancer [37]. Studies have shown that consumption of green pistachios (P.v.L.) significantly reduces total cholesterol [38] and LDL [39], while significantly increasing low-density lipoprotein. In a study on this subject, it was determined that the outer shell of the peanut contains high antioxidants [40].

Conclusion

As a result of this research, besides the advantages provided by the therapeutic properties of DOX, the cardiotoxicity caused by its use causes the production of free oxygen radicals. To reduce these effects, the use of natural or artificial antibiotics is needed. Therefore, the discovery of new antibiotics is of great importance.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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